

REMARKS/ARGUMENTS

The following remarks are responsive to the points raised by the Office Action dated December 17, 2008. In view of the following remarks, reconsideration is respectfully requested.

The Pending Claims

Claims 1-40 are pending, of which claims 23-40 are currently under examination, and claims 1-22 are withdrawn.

Rejections under 35 U.S.C. § 103

Claims 23-35, 37 and 38 were rejected under § 103 as unpatentable over Dudley et al., *J. Immunotherapy* 24: 363-373 (2001) (hereinafter, "Dudley 2001") or WO '97/05239 (hereinafter, "WO '239") in view of U.S. Patent No. 6,447,767 to Slavin et al. (hereinafter, "Slavin") and Riddell et al., *J. Immunol. Method* 128: 189-201 (1990) (hereinafter, "Riddell"), and U.S. Patent 5,126,132 to Rosenberg (hereinafter, "Rosenberg").

Claims 36, 39, and 40 were rejected under § 103 as unpatentable over Dudley 2001 or WO '239 in view of Slavin, Rosenberg, and Riddell, as applied to claims 23-35, 37 and 38 above, and further in view of Kawakami et al. *PNAS* 91: 6458-6462 (1994) (hereinafter, "Kawakami") and Stevens et al. *J. Immunol.*, 154: 762-771 (1995) (hereinafter, "Stevens").

Each of these rejections is separately and respectfully traversed.

As an initial point, the Office has not set forth a *prima facie* case of obviousness. A *prima facie* case of obviousness requires that the cited combination of references teach or suggest each and every element of the claims. A *prima facie* case of obviousness has not been made with respect to independent claim 23 because the cited combination of references does not teach or suggest each and every element of independent claim 23.

Claim 23 is directed to a method of promoting the regression of a cancer in a mammal comprising, *inter alia*, administering T cells which have undergone *one* cycle of rapid expansion. The Office Action states (page 5, 2nd par.) that "[a]ll of the claimed elements were known in the prior art." This is simply incorrect. None of the cited references teach or

suggest a method of promoting the regression of a cancer in a mammal comprising administering T cells which have undergone *one* cycle of rapid expansion, as claimed in claim 23. Because none of the cited references teach or suggest a method comprising administering T cells which have undergone *one* cycle of rapid expansion, as claimed, the obviousness rejection cannot be maintained.

Moreover, as stated in the last-filed response, and as supported by the Declaration under 37 C.F.R. § 1.132 by Dr. Mark E. Dudley (hereinafter, "Dudley Declaration") filed on October 17, 2008, the presently claimed method is also patentable over the cited references in view of several secondary considerations that would rebut any alleged *prima facie* case of obviousness (MPEP § 2145). Specifically, the presently claimed method is patentable because it answers a long-felt need, successfully treats cancer patients as compared to the repeated failure of other methods, and provides unexpectedly superior results over the prior art.

The presently claimed method answers a long-felt need in the art to treat patients. As explained by the Dudley Declaration, T-cells underwent *multiple* cycles of rapid expansion in Dudley 2001 and Yee et al., *PNAS*, 99: 16168-73 (2002) (hereinafter, "Yee"). As explained in Dudley 2001 (see, e.g., p. 370, right col.; p. 371, left col.), Yee (p. 16172, right col.; page 16171, right col.), and the Dudley Declaration (Dudley Dec. ¶¶ 5 - 8), the T-cells of Dudley 2001 and Yee failed to persist in the bloodstream of patients and provided poor objective clinical results as measured by RECIST or WHO criteria. In contrast, the claimed method, in which T-cells undergo *one* cycle of rapid expansion, successfully produces positive objective clinical results in patients as shown, for example, in the study described in Example 1 of the instant application (see also Dudley et al. *Science* 298: 850-854 (2002) (hereinafter, "Dudley 2002") and Dudley et al., *J. Clin. Oncol.*, 26(32): 5233-5239 (2008) (hereinafter, "Dudley 2008")) (Dudley Declaration, ¶¶ 10-13). Accordingly, the presently claimed method is patentable because it answers a long-felt need in the art to treat patients.

In addition, the presently claimed method successfully treats patients as compared to the repeated failure of other methods. As explained above, other methods (e.g., Dudley 2001 and Yee) use multiple cycles of rapid expansion, and the T-cells fail to persist in the bloodstream of patients and provide poor objective clinical results. In contrast, the claimed method, in which T-cells undergo one cycle of rapid expansion, produce positive clinical

results in this patient population and, therefore, succeed where other methods have repeatedly failed. Accordingly, the presently claimed method is also patentable because it successfully treats patients after the repeated failure of other methods.

Moreover, the presently claimed method is also patentable because it provides unexpectedly superior objective clinical responses as compared to methods in which the T-cells have undergone *multiple* cycles of rapid expansion. As evidenced by the Dudley Declaration, based on the poor objective clinical results obtained in Dudley 2001 and Yee, one of ordinary skill in the art at the time the instant application was filed would *not* have expected that T-cells that had undergone *only one* cycle of rapid expansion, as claimed, would result in a positive, objective clinical response in patients (Dudley Declaration, ¶¶ 3-9). In response to the repeated failure of other methods using multiple rounds of rapid expansion, one of ordinary skill in the art would logically attempt to improve the persistence and effectiveness of the T-cells by *increasing* the number of cycles of rapid expansion, not *decreasing* the number of cycles to one, as claimed.

However, contrary to the seemingly logical choice to increase the number of rounds of rapid expansion, the inventors have, instead, found that reducing the number of cycles of rapid expansion to *one* cycle, as claimed, successfully produces positive, clinical results. Therefore, contrary to the expectations of one of ordinary skill in the art at the time the instant application was filed, a method in which T-cells undergo *one* cycle of rapid expansion, as claimed, has unexpectedly produced positive, objective clinical results, as evidenced by the Dudley Declaration and the data published in the Dudley 2002 and 2008 references referred to therein. The positive, objective clinical results include tumor regression in virtually all visceral and soft tissue sites and superior persistence of the transferred cells in the blood (Dudley Declaration, ¶¶ 10-13). Thus, reducing the number of cycles of expansion to one, as claimed, would be counterintuitive to one of ordinary skill in the art, and illustrates a paradigm shift that is an important contribution over the prior art. Accordingly, the obviousness rejection cannot be maintained.

The Office Action has not adequately addressed the applicants' arguments and evidence in support of patentability. The Office Action alleges that the arguments are not persuasive because the applicants have allegedly merely argued against the references individually and not the combination of the references. The Office Action further argues that

a specific teaching, suggestion or motivation are not required to support an obviousness rejection, and that obviousness does not require absolute predictability, only a reasonable expectation of success. The Office Action further alleges that the effects of the claimed method are not surprising because, at the time the invention was made, one of ordinary skill in the art would know that administering to the mammal nonmyeloablative lymphodepleting chemotherapy was a routinely used method to induce donor specific tolerance in a method of treating a cancer patient. The Office Action further alleges that one of skill in the art would expect that administering nonmyeloablative lymphodepleting chemotherapy prior to administering T cells would provide better clinical responses.

MPEP § 2145 explains the legally proper procedure for evaluating obviousness: Assuming, *arguendo*, that a *prima facie* case of obviousness is established (and, as set forth above, the applicants submit it has not been established), the burden shifts to the applicant to come forward with arguments and/or evidence to rebut the *prima facie* case. Rebuttal evidence and arguments can be presented in the specification, by counsel, or by way of an affidavit or declaration under 37 CFR 1.132. Moreover, Office personnel should consider all rebuttal arguments and evidence presented by applicants (MPEP § 2145). The Office Action has not done this.

The counter-arguments by the Office ignore the applicants' arguments and rebuttal evidence in support thereof (in the form of the Dudley Declaration, Example 1 of the specification, and the Dudley 2002 and 2008 references) that the claimed method, in which the T-cells had undergone *only one* cycle of rapid expansion, provides *unexpectedly superior clinical results* over the methods described in the cited references. Thus, an additional issue, which was not addressed by the Office, is that the claimed methods produce unexpectedly superior results. Moreover, the Office Action also fails to consider the evidence that the Applicants have also presented with respect to the expectations of one of ordinary skill in the art, long-felt need, and the repeated failure of other methods in the form of the Dudley Declaration and the Dudley 2001 and Yee references referred to therein. Thus, the applicants have clearly rebutted any alleged *prima facie* case of obviousness.

The Office Action's comments with respect to arguing references individually, predictability, and motivation to modify or combine references fail to properly consider this rebuttal evidence. Although the Office Action alleges that the addition of nonmyeloablative

lymphodepleting chemotherapy does not provide surprisingly superior results, the Office Action completely fails to consider the fact that reducing the number of cycles of rapid expansion to *one*, as claimed, as opposed to increasing the number of cycles of rapid expansion, has produced surprisingly superior, objective clinical results, contrary to the expectations of one of ordinary skill in the art. The Office Action also fails to consider that the presently claimed method answers a long-felt need and successfully treats cancer patients as compared to the repeated failure of other methods.

The commonly accepted wisdom at the time the application was filed was to administer T cells that had undergone *multiple rounds* of rapid expansion (Dudley Declaration, ¶¶ 3-9). As explained by the Dudley Declaration, and as shown in Dudley 2001 and Yee, those methods repeatedly failed to produce objective, clinical results. Accordingly, one of ordinary skill in the art would have attempted to increase the number of rounds of rapid expansion, and would not have expected that administering T cells that had undergone *only one* round of rapid expansion would have resulted in superior, objective clinical responses. As explained in the Dudley Declaration, and as shown in Dudley 2002 and Dudley 2008, contrary to this expectation, administering T cells that had undergone *only one* round of rapid expansion did unexpectedly produce superior, objective clinical responses in patients (Dudley Declaration, ¶¶ 10-13) and answered a long-felt need in the art. Thus, because the claimed method answers a long-felt need, successfully treats cancer patients as compared to the repeated failure of other methods, and provides unexpectedly superior objective clinical responses as compared to the methods of Dudley 2001 and WO '239, the obviousness rejection cannot be maintained.

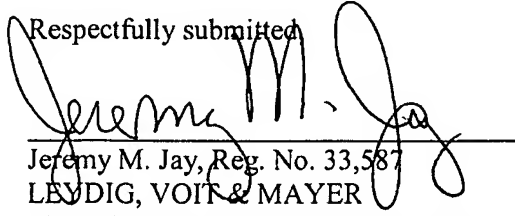
Because the Office Action has not set forth a valid reason as to why *all of* the rebuttal evidence presented by the Applicants fails to rebut any alleged *prima facie* case of obviousness, the obviousness rejection cannot be maintained.

Since independent claim 23 is patentable for the reasons set forth above, the dependent claims are also allowable because they depend from allowable independent claim 23.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted



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